Cerebral Palsy

The Correlation of Clinical and Pathological Observations

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• **Although the causes of cerebral palsy are well known, it is often difficult to assign a cause in specific cases. In some cases, the cause may have been determined on the basis of the history and findings, only to be found in error at autopsy.**

In four of the five cases of cerebral palsy reported herein, there was correlation between the clinical findings and the neuropathological findings. In the fifth case, before the patient died, the cause of brain damage was thought to be measles encephalitis; but neuropathological evaluation at autopsy indicated that the brain was microcephalic and inadequately developed as a result of genetic factors.

CEREBRAL PALSY, a term that has been established in medical literature during the past few years, includes a variety of disturbances affecting the neuromuscular system. The definition accepted by the American Academy for Cerebral Palsy[7] is as follows: "Cerebral palsy comprises the motor and other symptom complexes caused by a nonprogressive brain lesion (or lesions)."

Cerebral palsy may manifest itself in many ways, including spasticity, athetosis, tremor, rigidity, ataxia and combinations of these motor disturbances. Because of the brain damage which is present, there may be associated neurological disturbances such as mental deficiency and epilepsy and disturbances of sensation, speech, hearing and vision.

Incidence and Prevalence

The incidence of cerebral palsy is reported to be 5.9 per 1,000 live births. The actual prevalence of 1.52 per 1,000 population was reported in a study by Levin, Brightman and Burtt[5] with a maximum frequency in the age group 5 to 19 years. The peak was in the 5 to 9 year group (6.34 per 1,000) and the next highest in 10 to 14 group (5.0 per 1,000). Illingworth[3] said that there is a good agreement in reported statistics from British and Scandinavian sources, with a prevalence of 1 to 2.1 per 1,000 cases of cerebral palsy in school children.

Etiology

The causes of cerebral palsy are many. The etiological factors are usually divided into three groups: Prenatal, perinatal and postnatal. Among the factors responsible for prenatally determined cerebral palsy are hereditary, prenatal infection, prenatal anoxia, bleeding in the first trimester, multiple births, abruptio placentae, placenta previa, toxemia and diabetes.

Perinatal factors that have been considered as responsible for this condition include breech presentation, protracted or precipitate delivery, induced labor or improper application of forceps, narcotism, maternal anoxia, hypotension and blood factor incompatibilities. Prematurity is also a significant predisposing factor. In our experience in the cerebral palsy clinic at the University of California Medical Center, approximately one-third of the children with a diagnosis of cerebral palsy had a history of prematurity. This is in contrast to the incidence of prematurity in the State of California of about 7 per 100 live births. Postnatal factors include head injury, anoxia, infections of the central nervous system and toxic factors.

Unfortunately, the clinical impression of cause may not be accurate, for in individual cases of cerebral palsy only retrospective information is available, parents may not have all the facts, and a distorted history may not accurately determine the cause of the condition.

Prevention

In order to prevent cerebral palsy and its many serious handicapping effects it is important, of course, to know the cause or causes. Continued emphasis on the factors that are responsible for this condition may eventually lead to a diminution in the incidence and prevention of the many handicapping conditions associated with it.

A means of obtaining more accurate information with regard to etiology is by prospective studies with accurate tabulation of data during pregnancy and at delivery, with careful examination of the child at the time of delivery and during the period of motor development. Tabulation of such data might throw further light on the causes of cerebral

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palsy. Such a study is in progress under the auspices of National Institutes of Neurological Diseases and Blindness as a collaborative study carried out in many medical centers.[8] Although the data from the study will not be available for some time, it undoubtedly will lead to a clearer understanding of many of the factors associated with the production of cerebral palsy.

Neuropathology

Another approach to an understanding of etiological factors is by pathological examination of persons in whom a diagnosis of cerebral palsy has been made and in whom adequate clinical evaluation has been carried out. Early pathological reports of this condition were based on examination of persons who had died many years after the presumed causation and they are concerned mainly with descriptions of the observations at autopsy without correlation with clinical features or possible etiologic factors.

Crothers and Paine,[2] in reviewing the pathologic evidence on the causation of cerebral palsies, noted the controversy that has appeared in the literature with regard to the relative importance of brain hemorrhage and anoxia in the production of brain damage and subsequent cerebral palsy. They found it plausible that hemorrhage almost inevitably produces some anoxia in the area supplied by the vessels which bleed; and that anoxia may produce petechial hemorrhages is also generally accepted. Courville[1] considered anoxia the major cause of cerebral palsy and held that it is of much greater relative importance than frank trauma. In a study by Josephy[4] the term "birth injury" was applied to a variety of neonatal brain lesions, including mechanical injury, hemorrhage and other vascular disorders, as well as most of the effects of asphyxia. Towbin[10,11] classified the pathological process of cerebral palsy into three basic groups:

1. Cerebral palsy due to brain lesions which represent the sequelae of an antecedent systemic disorder of the fetus or newborn infant, including anoxia neonatorum, prematurity, erythroblastosis fetalis and septic states which would result in elective parenchymal necrosis, lobar sclerosis, cystic lesions, status marmoratus, hemorrhage, necrosis and kernicterus.

2. Cerebral palsy due to brain damage of local intracranial processes such as mechanical injury to the head either perinatally or postnatally, circulatory disorders such as thrombosis and embolism, and hydrocephaly. This results in meningeal hemorrhage, ischemia and infarcts, and in damage to motor cortex due to compression and thinning of the cerebral wall.

3. Developmental defects of the brain due to induced or hereditary influences which cause arrest of growth and differentiation and result in cerebral hypogenesis and dysgenesis.

Malamud[6] reported 162 cases as representative of brain damage acquired either at birth or during infancy and early childhood. He divided these cases into two groups: (a) Those with primary subcortical pathologic changes that were characterized either by status marmoratus of the striatum and thalamus or by primary sclerosis or cystic degeneration of the cerebral white matter, with or without focal encroachment of the cortex. There was a high correlation of a history of birth trauma with these lesions. (b) A group with primary cortical pathologic changes characterized by uniform atrophy of the involved gyri associated with widening of sulci. In 90 per cent of the cases in this group there was a history of normal birth and early development followed by an acute illness at some time during infancy or early childhood. The illnesses included meningitis, encephalitis and less definite conditions of febrile convulsions, diarrhea and septicemia.

Although it is recognized that certain cases of cerebral palsy are due to anomalies of the brain, there is question as to its relative frequency and that of birth trauma as causative factors. There is also question as to whether the anomalies represent true maldevelopment from inception of the fetus or whether they are due to prenatal damage to the developing brain.

REPORTS OF CASES

Cerebral Palsy Due to Prenatal Influence

CASE 1. The patient had a confusing history and was considered to have cerebral palsy due to postmeasles encephalitis until the results of autopsy were available. She was born after pregnancy characterized by bleeding at two months, with normal delivery three weeks after the expected date of confinement. The child weighed 7 pounds 4 ounces. She did not breathe immediately and oxygen was administered for about 5 minutes. She appeared to develop normally until 10½ months, when she had measles.

The family history was of interest in that an older brother was blind since birth and was mentally deficient; a maternal cousin was mongoloid.

Upon physical examination at 18 months of age, microcephaly and ataxia were noted. The developmental quotient was reported as 14. While under observation for the next 14 months, she made slight improvement in that she developed the ability to hold up her head and sit in a Baby-Tenda if secured. At 2 years of age she had a grand mal convulsion, although a subsequent electroencephalogram was reported as within normal limits. The child was eventually admitted to Sonoma State Hospital where she died at 6 years of age.

The brain weighed 940 gm. It was symmetrical, moderately reduced in size, with a normal convolutional pattern, normal meninges and blood vessels.

Coronal sections showed normal proportions of grey and white matter with no evidence of demyelinating lesions (Figure 1). The ventricular system was patent and of average size. There were no gross changes either in the brain stem or the cerebellum. The microscopic examination did not show any distinct changes. There were no signs of malformation or lesions which could be attributed to measles encephalitis.

The neuropathological diagnosis was microcephaly of moderate degree without gross anomalies (probably genetic microcephaly).

This case demonstrates the unreliability of the history in an attempt to determine the cause of brain maldevelopment. If the history had not stressed the illness of measles at the end of the first year, there might have been more emphasis on the family history.

Cerebral Palsy Due to Brain Lesions Occurring at the Time of Birth

A large number of cases of cerebral palsy occur in the fetus and newborn whose various brain structures are normally formed but have been subjected to injury or noxious influences at the time of birth. The following report illustrates the changes observed in the brain of a child in whom there was difficulty in initiating respiration.

CASE 2. The patient was apparently normally delivered after an uneventful pregnancy, but was quite cyanotic and was not expected to live; for the first two or three days of his life he had generalized convulsions. He remained in the hospital for one month because of feeding difficulties.

At the age of 2 years he was unable to sit by himself and did not talk. On examination at that time he was found to be microcephalic and there was evidence of severe tension athetosis in all extremities. On the Gessell Developmental scale he was found to have a developmental level of 2 months, at a chronological age of 2 years 5 months. An electroencephalogram was considered normal. The child was eventually admitted to Sonoma State Hospital and continued to be a difficult feeding problem. He died at the age of 7 years as a result of bronchopneumonia.

At autopsy the brain weighed 726 grams and was asymmetrical as a result of atrophy of the left occipital lobe (Figure 2). The convolutional pattern appeared to be relatively normal but there was a distinct discrepancy on the left side between a large temporal and a small occipital lobe, and the right pyramidal tract appeared smaller than the left one. There was diffuse crowding of the gyri. On section

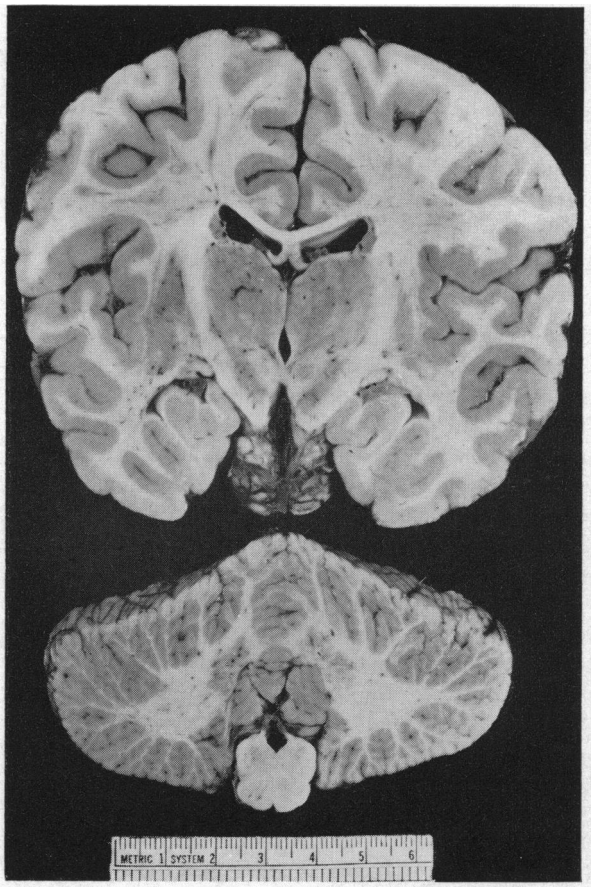

Figure 1.—(Above) Normal proportions of gray and white matter, no evidence of demyelinating lesions; (below) No gross changes in brain stem or cerebellum.

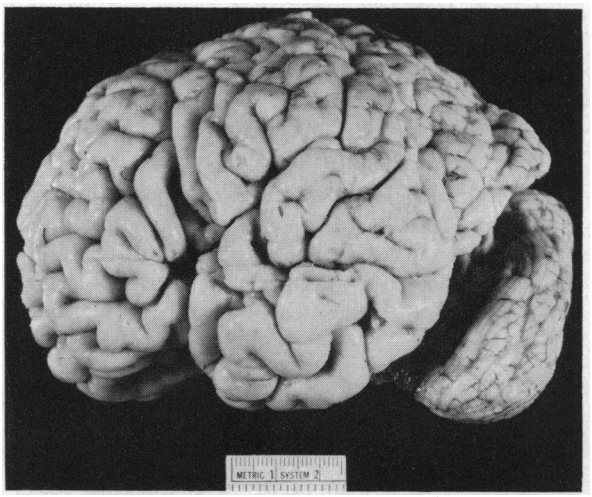

Figure 2.—Small brain, atrophy of the left parieto-occipital region.

there was a striking disproportion between relatively abundant cortex and pronounced reduction in the white matter (Figure 3). There was decided atrophy of the corpus callosum; the lateral ventricles were enlarged. In some areas there was additional cortical

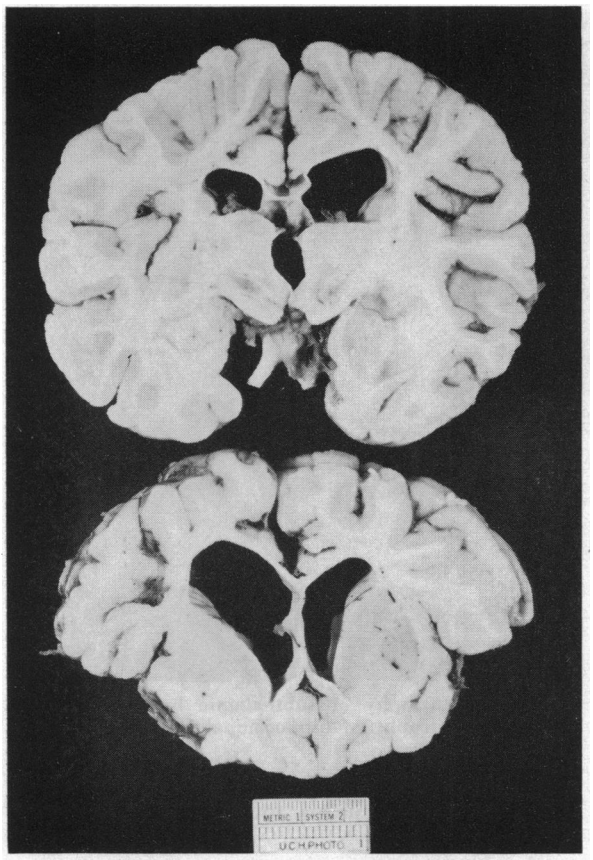

Figure 3.—(Above) Disproportion between relatively abundant cortex and marked reduction in white matter; enlargement of lateral ventricles. (Below) Vague discoloration of the basal ganglia suggesting status marmoratus.

atrophy, irregularly distributed. The thalamus was decidedly atrophic bilaterally and contained faint traces of a status marmoratus. The temporal horn was considerably enlarged; the fornix was underdeveloped and there was a suggestion of hippocampal atrophy bilaterally. Pronounced enlargement of the third ventricle was noted. The midbrain stem structures were not appreciably involved except for the atrophy of the pyramidal tracts. There was no gross change in the cerebellum.

Microscopic section showed diffuse sclerosis of the white matter associated with irregular encroachment of the cortex in the form of focal lower layer degeneration mushrooming or radial scars. In the basal ganglia there was a characteristic status marmoratus of caudate nucleus, putamen and thalamus, the latter being most severely degenerated.

Features of the case were diffuse sclerosis of white matter, sclerotic microgyri of cortex and status marmoratus. According to Towbin,[11] sclerosis of white matter and status marmoratus are due to anoxia. However, Schwartz,[9] Malamud[6] and others agree that such degeneration of white matter and the pathologic conditions referred to as status marmoratus are due to mechanical circulatory disturbances in the Galenic venous system accompanying birth trauma. While anoxia certainly played a significant part in the clinical manifestations in Case 2, it is impossible to state whether anoxia was responsible for all the symptoms or followed traumatic damage to the brain.

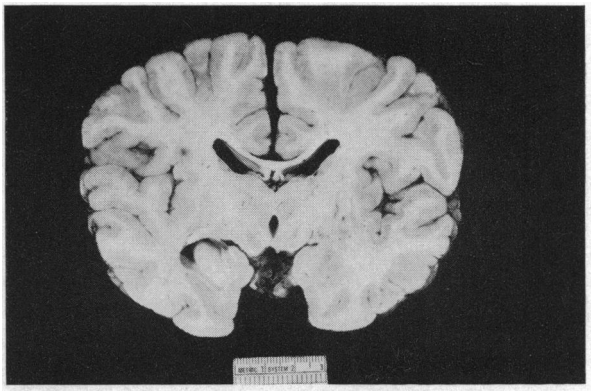

Figure 4.—Status marmoratus of basal ganglia and thalamus.

CASE 3. The patient was born 2 months prematurely of a diabetic mother while she was in diabetic coma. He weighed 5 pounds 5½ ounces at birth and remained in the hospital for one month with a question of birth injury. This child developed very slowly; he was never able to hold his head up alone nor to sit alone. He was difficult to feed and never developed speech. He was completely helpless throughout his life and the diagnosis was cerebral palsy, tension athetosis and mental deficiency. He died at the age of 7 years following an intercurrent infection of the respiratory tract.

The brain weighed 1,180 grams after fixation. It was of average size and symmetrical. The leptomeninges were thin, the basal vessels delicate. The brain showed a tendency to bulkiness in the frontal and temporal lobes. There was no evidence of cortical atrophy, and no change in the stem or cerebellum.

Coronal sections showed no evidence of cortical atrophy and no distinct change in the white matter (Figure 4). The ventricular system was of normal size, except for mild enlargement of the anterior horns. A pronounced status marmoratus of the basal ganglia and thalamus was evident, and a network of whitish fibers was present in these nuclei, somewhat more pronounced on the right side. The following areas were involved: The head, dorsal part of the body, and the major part of the tail of the caudate nuclei, the dorsal fourth of the anterior part of the putamen and, posteriorly, the dorsal two-thirds of the lentiform part of the putamen, especially on the right; the anterior halves of the dorsomedial thalamic nuclei and, sparing the re-

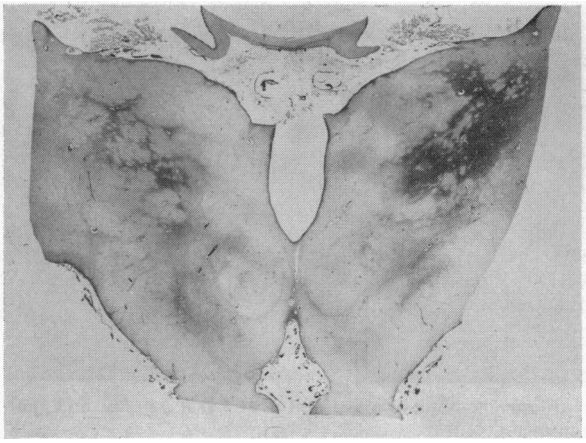

Figure 5.—Holzer stain: gliosis in the form of status marmoratus in the thalamus. (Macro slide ×5.)

mainder of the medial nuclei, involving severely the lateral group of thalamic nuclei and the pulvinar. There were no changes in Ammon's horn. The body of the corpus callosum was moderately narrowed. There were no gross changes in the cerebellum. The pyramids were somewhat reduced in size.

Microscopic Examination (Figure 5). The lesions in the caudate nucleus, putamen and thalamus consisted of an interlacing pattern of glial fibers in the Holzer preparation, with focal loss of neurons and increase in glial nuclei in Nissl-stained specimens and finely medullated fibers in the Weil-stained sections. Between the lesions, there were nests of preserved nerve cells. In the globus pallidus, there was a more diffuse gliosis. A milder gliosis was seen in the centromedial areas of the hypothalamus, in the vicinity of the substantia nigra, in the cerebral white matter and in the body of the corpus callosum. There were no changes in the cerebral cortex, brain stem, cerebellum or medulla, including the pyramidal tracts.

The pathologic changes in this case were limited almost entirely to the basal ganglia and were characteristic of status marmoratus. The relationship of the mother's diabetes and toxemia to this condition can only be conjectured. However, the mother's illnesses undoubtedly led to the premature birth of her child which could have a significant influence on factors leading to brain damage, much the same as in Case 2.

The following case is an example of hyperbilirubinemia resulting in kernicterus.

CASE 4. The patient was the product of the second pregnancy of an Rh-negative mother whose first child was normal. Following birth (weight 7 pounds 8 ounces) jaundice developed in the baby and the result of a Coombs test was positive. The infant was given several transfusions but not a replacement

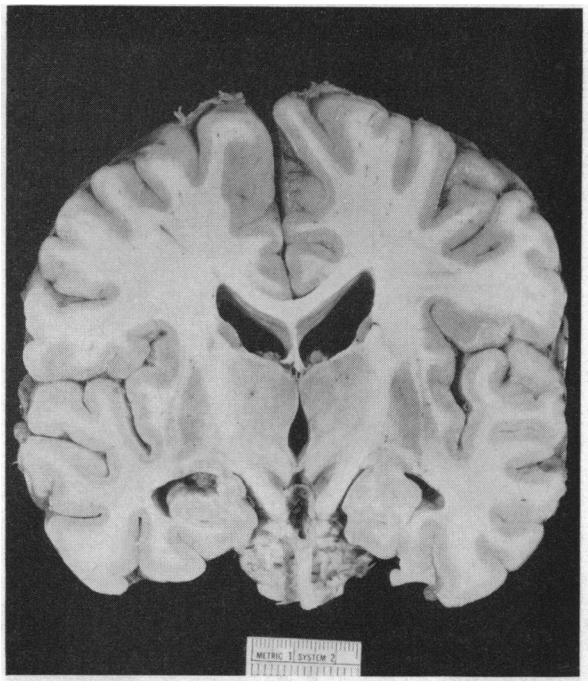

Figure 6.—Atrophy of subthalamic body and globus pallidus and atrophy of hippocampal formation.

transfusion. He was rigid and opisthotonic in the neonatal period and his motor development was extremely retarded.

On examination at 7 months of age he was fairly well nourished but completely helpless and showed no interest in his environment. Bilateral internal squint was present. He was unable to hold up his head; muscle tone varied from some increase to moderate hypotonicity; and mild tremors of the hands were present at times. The deep reflexes were equal and active in the arms; knee jerks were increased. Babinski's sign was positive bilaterally. Developmental tests were attempted but the child did not show any ability, even up to the 3-month level. An electroencephalogram at one year of age was reported as compatible with generalized cerebral dysfunction. No abnormality was noted in an x-ray film of the skull. The patient died at the Sonoma State Hospital at the age of 6 years 9 months.

The brain weighed 1,077 grams after formalin fixation. It was symmetrical and, with the exception of mild irregularities of its convolutional pattern and an exposed insula, there were no gross abnormalities. There was no evidence of atrophy of the cortex. However, the cerebellum was distinctly atrophic, firm and small relative to the size of the cerebrum. The optic pathways were grossly normal.

Coronal sections (Figure 6) showed normal outlines of all structures. The lateral ventricles were slightly but symmetrically dilated. The most striking changes were:

Figure 7.—Demyelinization and gliosis in globus pallidus and subthalamic body. Weil stain. (Macro slide ×5.)

1. Symmetrical bilateral atrophy of the globus pallidus, which was unusually pale, particularly in its internal division;
2. The subthalamic bodies were difficult to identify, probably because of atrophy;
3. The thalamus seemed pale;
4. There was a distinct atrophy of the dentate area of the hippocampus bilaterally, with corresponding enlargement of the temporal horns.

There were no gross changes in the brain stem. The cerebellum showed severe generalized atrophy of the folia, but differed in severity in different parts. The dentate nucleus and the inferior olivary nuclei were, however, grossly normal.

Microscopic Examination (Figure 7). The most significant lesions were bilateral degeneration and gliosis in the globus pallidus, the subthalamic body and the dentate area of the hippocampus. The latter included the dentate fascia, the end plate and the dorsal cell band. There were mild lesions in other areas, such as parts of the cerebral cortex, the medial nucleus of the thalamus, the mammillary body, the cerebellum and the inferior olives. The pathologic changes were unusual since common findings in kernicterus are confined to the pallidal, subthalamic and hippocampal areas. However, it is accepted that other parts of the brain may be involved occasionally.

Cerebral Palsy Due to Postnatal Brain Damage

CASE 5. The patient developed normally until 6 weeks of age at which time his skull was fractured in a fall from a perambulator. A subdural hematoma was observed and an attempt was made to evacuate it. Subsequent progress of the patient was extremely slow.

When the patient was 8 months of age air contrast roentgen studies were done and the parents were informed that there was evidence of a great deal of damage to the brain tissue. At 13 months, when

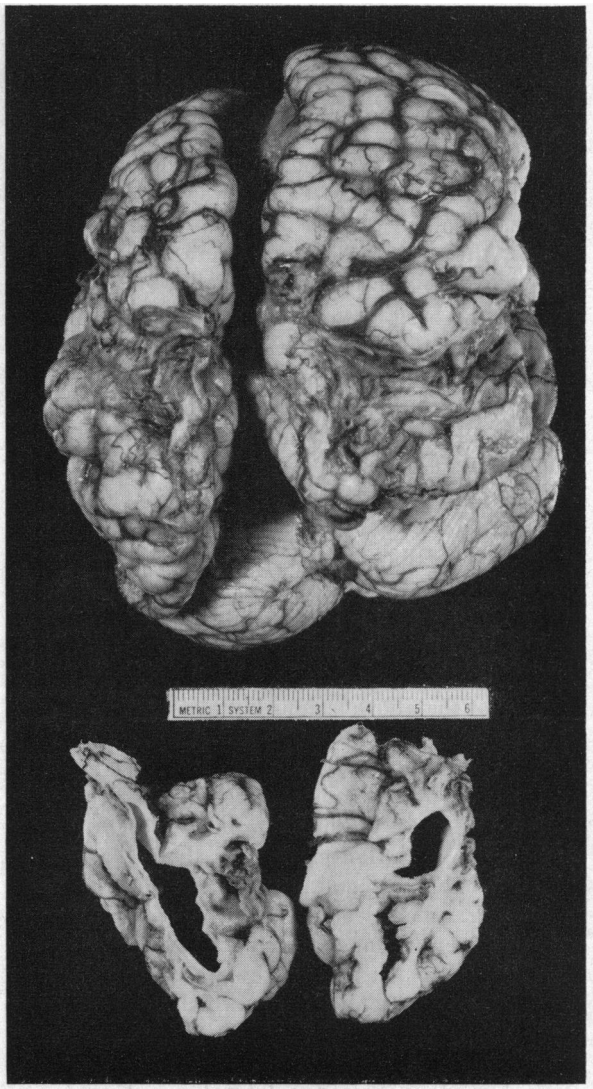

Figure 8.—Small, asymmetrical brain, left hemisphere smaller than right, showing extensive areas of chronic encephalomalacia in the parieto-occipital areas—(above) external surface; (below) coronal section.

the patient was seen in the Cerebral Palsy Clinic at the University of California Medical Center, he was unable to hold up his head or to sit up. He showed little reaction to his environment. His head was 42 cm. in circumference. The extremities were all moderately spastic. Deep reflexes were increased and Babinski's sign was positive bilaterally. Developmental tests were attempted, but no ability above the 1-month level was demonstrated. The child was eventually admitted to Sonoma State Hospital where he died at the age of 7 years 10 months. A note from Sonoma State Hospital indicated that the patient was blind. There was asymmetry of the body, with the right side of the chest larger than the left. He was spastic in all four extremities and required bottle feeding.

At autopsy strong fibrous adhesions binding the dura to portions of the brain were noted. A cystic softening process extensively involved the cerebral hemispheres; it was most prominent over the mid-lateral aspects.

After formalin fixation, the weight of the brain was 450 gm. (Figure 8). It was very small and asymmetrical, the left hemisphere being somewhat smaller than the right. There were many extensive destructive lesions, localized as follows:

1. In the base of the frontal lobes bilaterally but more extensively on the left side;
2. Bilateral parasylvian lesions exposing the insula with extensive destruction of the temporal, frontal and parietal opercula;
3. Bilateral basitemporo-occipital lesions except the hippocampal gyri, and
4. A parasagittal central lesion on the left side.

Coronal sections (Figure 8) confirmed the presence of these lesions, which appeared to be residual infarcts in vascular areas (middle, posterior and anterior cerebral). In addition, there was a diffuse reduction in white matter, most pronounced in the vicinity of the above lesions but also spread beneath the more normal cortex, and decided atrophy of the corpus callosum. The basal ganglia showed a change in the head of the caudate nucleus bilaterally that resembled status marmoratus, and there was suggestion of a similar change in the thalamus but without visible change in the putamen or any of the remaining subcortical nuclei. The peduncles were small bilaterally and the lateral ventricles were greatly dilated. The optic pathways appeared normal except for the optic radiations, which were obviously destroyed in the vicinity of the occipital cortical lesions. A part of the dura enclosed with the specimen showed organized subdural membranes, apparently bilaterally.

Microscopic Report. The cerebral lesions were severely destroyed areas in which the nervous tissue was virtually replaced by cyst formation and gliosis, and in which considerable calcium had been deposited within microglia and gitter cells in the areas of necrosis. Grey matter and white matter were equally affected. The walls of the meningeal vessels were frequently thickened, hyalinized and calcified. Status marmoratus of moderate degree was evident in parts of the caudate nucleus, putamen and thalamus. Subdural hematomas were in a very chronic stage of fibrous organization. The hippocampus showed focal areas of scarring in Sommer's sector and the end-plate region. The cerebellum also contained focal areas of atrophy of both Purkinje and granular layers.

This case was considered unusual in that, in addition to the post-traumatic chronic subdural hematomas, extensive destruction of the underlying brain tissue had occurred which appeared to be owing to vascular complications—arterial or venous. Supporting that etiologic surmise was the status marmoratus, which is rare in cases of postnatal trauma although a common sequel to birth trauma.

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